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Cardiorespiratory fitness levels and their association with cardiovascular profile in patients with rheumatoid arthritis: a cross-sectional study

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Abstract

Objective. The aim of this study was to investigate the association of different physical fitness levels [assessed by the maximal oxygen uptake (VO₂max) test] with cardiovascular disease (CVD) risk factors in patients with RA.

Methods. A total of 150 RA patients were assessed for cardiorespiratory fitness with a VO₂max test and, based on this, were split in three groups using the 33rd (18.1 ml/kg/min) and 66th (22.4 ml/kg/min) centiles. Classical and novel CVD risk factors [blood pressure, body fat, insulin resistance, cholesterol, triglycerides, high-density lipoprotein (HDL), physical activity, CRP, fibrinogen and white cell count], 10-year CVD risk, disease activity (DAS28) and severity (HAQ) were assessed in all cases.

Results. Mean VO₂max for all RA patients was 20.9 (S.D. 5.7) ml/kg/min. The 10-year CVD risk ($P = 0.003$), systolic blood pressure ($P = 0.039$), HDL ($P = 0.017$), insulin resistance and body fat (both at $P < 0.001$), CRP ($P = 0.005$), white blood cell count ($P = 0.015$) and fibrinogen ($P < 0.001$) were significantly different between the VO₂max tertiles favouring the group with the higher VO₂max levels. In multivariate analyses of variance, VO₂max was significantly associated with body fat ($P < 0.001$), HDL ($P = 0.007$), insulin resistance ($P < 0.003$) and 10-year CVD risk ($P < 0.001$), even after adjustment for DAS28, HAQ and physical activity.

Conclusion. VO₂max levels are alarmingly low in RA patients. Higher levels of VO₂max are associated with a better cardiovascular profile in this population. Future studies need to focus on developing effective behavioural interventions to improve cardiorespiratory fitness in RA.

Key words: exercise, physical activity, cardiorespiratory fitness, cardiovascular disease, inflammation, rheumatoid arthritis.

Rheumatology key messages

- Cardiorespiratory fitness is alarmingly low in RA patients.
- Cardiovascular profile and 10-year cardiovascular disease risk are both deteriorated in RA patients with low fitness levels.
- Cardiorespiratory fitness may be a good surrogate cardiovascular disease marker in RA.

Introduction

RA is associated with an increased risk of cardiovascular disease (CVD) [1], attributed both to the deleterious effects of inflammation on the vasculature and to the increased prevalence of traditional CVD risk factors [2-5]. Increased physical activity and/or exercise may be associated with an improved CVD risk profile in both healthy and diseased populations; this is indicated by the robust inverse relationship of CVD morbidity and mortality with cardiorespiratory fitness, as measured by the gold standard method, the maximal oxygen uptake (VO₂max) test [6]. Patients with RA have significantly lower levels of VO₂max compared with healthy counterparts [7], but the association of VO₂max with CVD risk has never been investigated in this population. The aim of the present cross-sectional study was to investigate the association of VO₂max with both traditional and novel CVD risk factors and 10-year CVD risk in a well-characterized population of patients with RA.

Methods

Participants

One hundred and fifty patients were recruited from the Dudley Group of Hospitals NHS Foundation Trust, UK. The study was approved by the Birmingham East, North and Solihull Research Ethics Committee, and volunteers signed informed consent after we provided a detailed verbal and written description of the procedures involved, according to the Declaration of Helsinki. Patients' records were reviewed before requesting participation. Inclusion criteria were: fulfilling the ACR RA criteria and being on stable treatment for at least 3 months. Exclusion criteria were: previous/present CVD (e.g. cardiomyopathies, arrhythmias), cerebrovascular disease, diabetes, restrictive/ obstructive lung disease, known malignancy, pregnancy, current infection, hyper- or hypothyroidism, recent joint surgery (preceding 6 months), amputation and functional comorbidities incompatible with VO₂max testing.

Procedures

Patients visited our laboratory after a 12-h overnight fast for collection of blood samples and recording of demographic, anthropometric and disease-related characteristics: standing height was measured with a Seca Stadiometer, body mass and composition via bioelectrical impedance (Tanita BC418-MA, Japan), disease activity via ESR, CRP and the 28 joint DAS DAS28, and disease severity via the Stanford HAQ. Classical and novel CVD risk profile included: triglycerides, total cholesterol, highdensity lipoprotein (HDL), low-density lipoprotein (LDL) (Vitros 5.1, USA), physical activity (International Physical Activity Questionnaire), glucose and insulin (Immunolite 2000 Analyser, USA) [from which the homeostasis model assessment (HOMA) was calculated], blood pressure, family history, smoking, CRP (Vitros 5.1 FS, USA), haemoglobin and white cell count (ADVIA 120, Germany) and fibrinogen (IL Futura Advance analyser, UK). Ten-year CVD risk was calculated using the Framingham score.

Participants returned within 3 days to perform an individualized VO₂max test protocol with electrocardiography (after taking into account their physical abilities and the American Heart Association guidelines) using a previously published protocol [8] and specific contraindications for terminating the test [9]. The VO₂max test was performed on a treadmill using a calibrated breath-by-breath system (Metalyzer 3B, Cortex, Germany). Based on the results of the VO₂max test, participants were divided into three groups, using the 33rd (18.1 ml/kg/min) and 66th (22.4 ml/kg/min) centiles [10]. To determine the number of participants needed per group, we used RA [8] and age-matched normal population VO₂max data, and calculated that 44 patients were needed per group (90% power and 5% alpha error level). To account for potential dropout, we recruited 150

patients (i.e. 50 per group). Given the relevant VO2max data from the general population [9], these groups reflected unfit vs moderately unfit vs average fitness groups, respectively.

Statistical analyses

Kolmogorov-Smirnov tests were performed to investigate the distribution of all variables. Accordingly, normally distributed variables are reported as mean (S.D.), whereas non-normally distributed variables as median [interquartile range (IQR)]. Chi-square analyses were conducted to investigate differences amongst the VO2max tertiles for categorical variables (e.g. gender and medication). One-way analyses of variance with Bonferroni correction for adjusting the number of multiple comparisons or Kruskal-Wallis tests were utilized, according to distribution, to investigate differences between VO2max tertiles. After controlling for age, gender and physical activity, multivariate analyses of variance with Sidak correction were initially utilized to investigate the association of VO2max levels (as a categorical variable for the three groups) with CVD risk factors. Thereafter, disease activity and severity variables were also utilized in the same models to investigate whether the association of VO2max with CVD factors and 10-year CVD risk persisted. For the multivariate analyses of variances, log transformations were conducted on all the variables that were not normally distributed. The adjusted mean differences (with 95% CI) were also reported for the variables that were significantly different. The level of significance was set at $P < 0.05$.

Results

Of the 150 patients who agreed to participate, 6 did not attend. Mean VO2max for the entire cohort was 20.9 (S.D. 5.7) ml/kg/min, and it was significantly different between the tertiles, that is, unfit: 15.4 (S.D. 1.9) vs moderately unfit: 20.2 (S.D. 1.3) vs average: 27.1 (S.D. 4.7) ml/kg/min ($P < 0.001$). Significant differences were detected between the tertiles in age (Table 1, $P = 0.035$) but not gender (Table 1, $P = 0.095$) or physical activity (Table 2, $P = 0.051$). The anthropometric and disease-related characteristics of the three RA groups appear in Table 1.

Table 1. Anthropometric and disease-related characteristics the total population and fitness subgroups

Characteristics	Total RA (<i>n</i> = 144)	Unfit (<i>n</i> = 47)	Moderately unfit (<i>n</i> = 48)	Average fitness (<i>n</i> = 49)	P-value
VO2max, mean (S.D.), ml/kg/min	20.9 (5.7)	15.4 (1.9)**	20.2 (1.3)**	27.1 (4.7)	<0.001
Age, mean (S.D.), years	54.4 (11.7)	54.7 (13.4)	57.3 (10.3)*	51.2 (10.6)	0.035
Gender: females, <i>n</i>	101	37	35	29	0.095
Anthropometric, median (IQR)					
Height, cm	.66 (1.59-1.71)	11.66 (1.59-1.71)	1.64 (1.59-1.73)	1.66 (1.61-1.72)	0.777
Weight, kg	76.8 (65.5-90.0)	86.3 (70.5-97.7)**	77.5 (70.5-86.8)*	69.2 (59.3-82.0)	<0.001
Fat-free mass, kg	49.0 (42.0-58.0)	49.0 (42.2-59.7)	47.0 (42.0-58.0)	49.0 (42.0-60.0)	0.944
RA characteristics, median (IQR)					
Disease duration, years	6.0 (3.0-10.0)	5.0 (2.0-6.5)	7.0 (4.0-14.5)*	5.0 (3.0-7.5)	0.046

DAS28	3.2 (2.3-4.5)	3.2 (2.1-4.6)	3.0 (2.3-4.0)	3.3 (2.3-4.5)	0.817
ESR, mm 1st h	11.0 (5.0-21.0)	19.0 (12.0-32.7)**	10.0 (7.0-21.5)*	5.0 (2.0-10.2)	<0.001
HAQ	0.58 (0.13-1.12)	0.79 (0.17-1.13)	0.52 (0.16-1.21)	0.35 (0.1-1.0)	0.617
Medication, n (%)					
DMARDs	73 (50)	24 (33)	28 (38)	21 (29)	0.414
Anti-TNFa	22 (15)	10 (45)	5 (23)	7 (32)	0.350
NSAIDs	50 (35)	17 (34)	15 (30)	18 (36)	0.948
Analgesics	57 (40)	20 (35)	18 (32)	19 (33)	0.709

P = differences between groups using either ANOVA or Kruskal_Wallis test. Normally distributed variables are reported as mean (S.D.) and non-normally distributed variables as median (IQR).

Significantly different from the Average fitness group: **P<0.001 and *P<0.05. Significant values are highlighted in bold. VO2max: maximal oxygen uptake; IQR: interquartile range; DAS28: DAS for 28 joints.

Associations between cardiovascular profile and VO2max

Significant differences between the three groups were detected in systolic blood pressure, HDL, insulin resistance and body fat, CRP, fibrinogen and white blood cell count, as well as 10-year CVD risk (Table 2).

Table 2. Classical CVD risk factors and 10-year CVD risk of the total population and fitness groups studied

Risk Factors	Total RA (n = 144)	Unfit (n = 47)	Moderately unfit (n = 48)	Average fitness (n = 49)	P-value
Classical risk factors, mean (S.D.)					
SBP, mmHg	132.6 (15.9)	134.4 (15.0)	135.6 (17.0)*	127.9 (14.7)	0.039
DBP, mmHg	81.0 (9.8)	80.4 (10.3)	82.8 (10.4)	79.6 (8.5)	0.4
Triglycerides, median (IQR), mmol/l	1.1 (0.8-1.6)	1.1 (0.8-2.1)	1.1 (0.0-1.7)	1.1 (0.8-1.4)	0.46
Cholesterol, mean (S.D.), mmol/l	5.0 (1.0)	5.1 (1.1)	5.1 (1.1)	5.0 (0.9)	0.916
HDL, median (IQR), mmol/l	1.4 (1.1-1.7)	1.2 (1.1-1.6)*	1.3 (1.2-1.6)	1.5 (1.2-1.8)	0.017
LDL, median (IQR), mmol/l	3.1 (2.5-3.6)	2.7 (2.4-3.7)	3.1 (2.5-3.6)	3.1 (2.6-3.5)	0.847
Glucose, median (IQR), mmol/l	4.6 (4.4-5.0)	4.6 (4.3-5.1)	4.7 (4.3-5.0)	4.6 (4.4-5.0)	0.772
HOMA, median (IQR), mmol/l	1.5 (0.9-2.3)	2.0 (1.4-2.4)*	1.5 (1.2-2.1)*	0.9 (0.6-1.7)	<0.001
BMI, median (IQR), kg/m ²	27.8 (24.2-31.5)	30.0 (26.0-35.0)**	27.9 (25.3-31.0)*	24.5 (22.1-27.8)	<0.001
Fat mass, median (IQR), %	35.0 (30.0-42.0)	41.0 (34.8-46.2)**	38.0 (32.2-42.7)**	30.0 (25.5-33.9)	<0.001
Physical activity, Metabolic Equivalent	3109.0 (1085.0-5812.5)	2102.5 (925.5-4447.5)	2830.5 (946.5-6018.7)	3549.0 (1782.0-9759.0)	0.051

Task_min/week, median (IQR)					
Smoking, n	17	6	4	7	0.912
Family history of CVD, n	62	23	20	19	0.995
Novel risk factors					
CRP, median (IQR), mg/l	3.6 (2.6- 8.6)	7.3 (3.0-10.7)*	4.5 (2.7-9.8)*	3.0 (1.7-4.5)	0.005
vWF, median (IQR), IU/dl	136 (108- 181)	138 (120-180)	143 (103-193)	129.0 (88-170)	0.329
White cell count, mean (S.D.), $\times 10^9/l$	6.7 (2.1)	7.3 (2.4)*	6.8 (1.9)	6.0 (1.8)	0.015
Haemoglobin, mean (S.D.), g/dl	13.3 (1.2)	13.1 (1.0)*	13.4 (1.2)	13.4 (1.4)	0.519
10 year CVD risk, %	7.0 (3.0- 13.0)	8.0 (4.0-15.2)	7.0 (4.0-12.9)	4.0 (2.0-7.0)	0.003

P = differences between groups using either ANOVA or Kruskal-Wallis test. Normally distributed variables are reported as mean (S.D.) and non-normally distributed variables as median (IQR). Significantly different from the Average fitness group: **P<0.001 and *P<0.05. Significant values are highlighted in bold. SBP: systolic blood pressure; DBP: diastolic blood pressure; IQR: interquartile range; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA: homeostatic model assessment; CVD: cardiovascular disease; vWF: von Willebrand factor.

Adjusted associations between cardiovascular profile and VO2max

Classical CVD risk factors: after correction for age, gender and physical activity, VO2max levels were significantly associated with body fat ($F_{1,107} = 16.7$, $P < 0.001$), HOMA ($F_{1,107} = 6.0$, $P = 0.003$) and HDL ($F_{1,107} = 5.3$, $P = 0.007$), but not systolic blood pressure ($P > 0.05$). After further adjustment for DAS28 and HAQ, VO2max was significantly associated with: (i) body fat ($F_{1,107} = 15.7$, $P < 0.001$), which was related to the differences reported between the average vs the unfit groups [mean difference 10.9% (95% CI 6.1%, 15.7%), $P < 0.001$] and average vs moderately unfit groups [mean difference 6.8% (95% CI 2.2%, 11.3%), $P = 0.001$] and (ii) HOMA ($F_{1,107} = 4.4$, $P = 0.016$) and HDL ($F_{1,107} = 5.6$, $P = 0.005$), which was related to the differences that were observed in the average vs the unfit group [mean difference HOMA 0.52 (95% CI 0.09, 0.95), $P = 0.012$ and HDL 0.23 (95% CI 0.05, 0.41) mmol/l, $P = 0.007$].

Novel CVD risk factors: after correction for age, gender and physical activity, VO2max levels revealed significant associations with CRP ($F_{1,109} = 3.8$, $P = 0.025$) and fibrinogen ($F_{1,109} = 18.5$, $P < 0.001$), but not white blood cells ($P = 0.087$). For CRP, this association was related to the differences between the average vs the unfit group [mean difference 0.78 (95% CI 0.09, 1.47) mg/l, $P = 0.021$]. Further correction for DAS28 and HAQ did not eliminate the significant association observed between VO2max levels and fibrinogen ($P < 0.001$): these associations were related to the differences between the unfit vs the average groups [mean difference 1.2 (95% CI 0.64, 1.80) g/dl, $P < 0.001$] as well as the moderately unfit vs the average groups [mean difference 0.64 (95% CI 0.06, 1.22) g/dl, $P = 0.024$].

Ten-year CVD risk: after adjustment for age, gender and physical activity, the levels of VO2max were significantly associated with the 10-year CVD risk ($F_{1,123} = 11.2$, $P < 0.001$), and further correction for DAS28 and HAQ in this model did not alter this association ($F_{1,123} = 10.8$, $P < 0.001$).

This was related to the differences that were detected between the average vs the unfit groups [mean difference 1.23 (95% CI 0.58, 1.88) years, $P < 0.001$] as well as the average vs the moderately unfit patients [mean difference 0.81 (95% CI 0.18, 1.45) years, $P = 0.007$].

Discussion

RA patients with higher VO₂max had a better CVD risk profile and a lower 10-year CVD risk compared with those with lower VO₂max levels. Substantial evidence demonstrates a strong inverse association between CVD morbidity and mortality and VO₂max [11, 12], highlighting the important role of fitness in health and longevity. RA patients repeatedly demonstrate significantly lower VO₂max levels compared with healthy counterparts, most likely related to their low levels of physical activity [7, 13] and increased disease activity/severity; for example, a fit RA patient may stop the test, potentially because of disease-related pain and physical dysfunction and not because of cardiorespiratory limitations. The low overall VO₂max levels observed in this study is an alarming finding that could be linked with the increased incidence of CVD-related death in RA; however, appropriate longitudinal studies are necessary to confirm this. Our results suggest significant differences between RA patients classified according to fitness level with respect to a variety of classic and novel CVD risk factors, as well as their 10-year CVD risk. As such, it seems reasonable to suggest that increased cardiorespiratory fitness may provide a measure of protection against CVDs in this population, which is similar to what is seen in the normal population [14, 15] and in other rheumatic diseases [16].

Further analyses have demonstrated that, after controlling for disease activity and severity, VO₂max levels are significantly associated with body fat, HDL and insulin resistance. RA patients experience a condition termed rheumatoid cachexia, which is characterized by a significant increase in adiposity and decreased muscle mass; as such, at the same weight a patient with RA may have an altered body composition compared with a normal healthy individual that favours an inferior cardiovascular profile [17]. This condition seems to be mediated by both inflammation and physical inactivity [17]. Studies in RA have previously shown that obesity is associated with both low HDL and insulin resistance [18]. Moreover, inflammation, which is overexpressed in both obesity and RA, affects glucose metabolism and the enzymes fundamental to HDL metabolism, promoting the development of insulin resistance and atherosclerosis [19]. The interplay of these factors with physical inactivity may in part explain the increased incidence of CVD in RA.

Exercise is the predominant intervention for increasing VO₂max. Even in a disease such as RA, which is characterized by significant disability, pain and fatigue, exercise is recommended; in fact, it can even ameliorate disease-related symptoms [20] and the calculated risk for CVD. Therefore, RA patients can and should exercise, but they consistently report lower levels of fitness compared with the healthy population [7, 16]. The effects of exercise on improving disease activity and cardiovascular risk factors have also been shown in axial SpA, another chronic inflammatory joint disease [21]. Research investigating ways of increasing and maintaining physical activity and reducing sedentary behaviour in RA patients is necessary.

This study is limited by not evaluating VO₂max levels of an equivalent age- and gender-matched population, its cross-sectional design and the non-inclusion of patients with pulmonary fibrosis/nodules or other significant extraarticular features (as well as by not keeping detailed records of non-included patients). Patients with poor mobility were also excluded, possibly introducing a positive bias in the present study. This would suggest that we have selected the fittest RA patients herein; even so, we demonstrated that their VO₂max levels were alarmingly low. Nevertheless, this is the first study that has explored the associations between VO₂max and CVD risk

factors with such a large sample of RA patients using appropriate power calculations and adjustment for several potential confounders. We conclude that, overall, VO₂max levels are low in both female and male RA patients, and that lower VO₂max levels are associated with inferior CVD profile and higher 10-year CVD event risk.

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